Case Report

SEVERE HYPERCALCEMIA SECONDARY TO PARAFFIN OIL INJECTIONS IN A BODYBUILDER WITH SIGNIFICANT FINDINGS ON SCINTIGRAPHY

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ABSTRACT

Objective: Non-parathyroid hormone (PTH) mediated hypercalcemia in young patients is rare. It encompasses a broad differential including malignancy, granulomatous diseases, Addison disease, and toxicity of vitamin A and D. We present an unusual case of non-PTH mediated hypercalcemia in a previously healthy bodybuilder, secondary to multifocal granulomatous disease from paraffin oil injections.

Methods: The patient was evaluated with laboratory tests including serum calcium, 25-hydroxyvitamin D, 1,25-hydroxyvitamin D, parathyroid hormone, and parathyroid hormone-related peptide. Imaging studies such as thorax computed tomography and bone scans were also performed.

Results: A 31-year-old male bodybuilder presented with severe hypercalcemia (corrected calcium 3.1 mmol/L) and renal failure (creatinine 840 μmol/L), with suppressed PTH 1.0 pmol/L (normal, 1.6 to 6.9 pmol/L), and 1,25-vitamin D 205 pmol/L (normal, 60 to 208 pmol/L). He had used anabolic steroids for bodybuilding purposes for 8 years, with the possibility that he may also have used paraffin oil injections. Computed tomography imaging along with patient history suggested multiple paraffinomas in the pectoralis muscles causing granulomatous foreign body reaction as a potential cause for his hypercalcemia. He was prescribed a trial of prednisone, but he discontinued it due to symptoms of acne. Unfortunately, due to poor adherence with medical direction, management of his hypercalcemia remains challenging with inconsistent use of steroids and pamidronate infusions.

Conclusion: Granulomatous foreign-body reactions are a rare side effect of paraffin oil injections used for muscle augmentation. These can lead to serious long-term side effects of severe hypercalcemia and renal failure, as seen in our patient. Prognosis is generally poor, with long term steroids as the preferred treatment. **(AACE Clinical Case Rep. 2020;6:e234-e238)**

Abbreviations:
CT = computed tomography; **CYP24A1** = 24-hydroxylase; **ED** = Emergency Department; **PTH** = parathyroid hormone

INTRODUCTION

Non-parathyroid hormone (PTH)-mediated hypercalcemia in young men is rare and can be caused by a number of different etiologies. These causes of hypercalcemia include thyrotoxicosis, Addison disease, pheochromocytoma, vitamin A and vitamin D toxicity, as well as various forms of granulomatous disease such as sarcoidosis and tuberculosis (1). Many times, the underlying cause is apparent after initial investigations. Occasionally, however, the cause of hypercalcemia may be more difficult to

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ascertain. In this case report, we describe the findings of a 31-year-old body builder with severe non-PTH mediated hypercalcemia and resulting renal failure and no obviously identifiable cause for his hypercalcemia found on standard investigations.

CASE REPORT

A 31-year-old bodybuilder initially presented to the Emergency Department (ED) with a 1 week history of bilateral lower limb edema and hypertension (blood pressure 170/104 mm Hg). He was previously healthy and on no prescription medications. Consistent with the presentation of nephrotic syndrome, he was found to have low albumin at 23 g/L (normal, 35 to 40 g/L), creatinine of 115 μmol/L and urinalysis with 3+ protein. This was in the setting of initiating a new steroid drug for the purpose of bodybuilding, in addition to taking Arimidex (anastrozole) and Equipoise (boldenone undecylenate). He had been using anabolic steroids daily for 8 years. The work-up in hospital for secondary causes of kidney injury was negative, including normal urine and serum protein electrophoresis, perinuclear antineutrophil cytoplasmic antibodies (p-ANCA) <2 RU/mL, antineutrophil cytoplasmic antibodies (c-ANCA) <2 RU/mL, anti-double strand deoxyribonucleic acid <10 IU/mL, anti-cyclic citrullinated peptide <5 RU/mL, anti-glomerular basement membrane <2 RU/mL, rheumatoid factor <21IU/mL, nonreactive hepatitis C, hepatitis B, and human immunodeficiency virus serology. His serum creatinine improved with intravenous fluids and he was discharged on amlodipine 5 mg daily for blood pressure management and advised to discontinue all anabolic steroids.

He returned to the ED with hypercalcemia and acute renal failure (calcium 3.01 mmol/L, albumin 33g/L, creatinine 840 μmol/L; Table 1). He denied intake of any other nonprescription medications or supplements and had discontinued anabolic steroids. His dietary calcium intake consisted of cheese 2 to 3 times per week and 2 liters of milk per week. There was no history of excessive sun exposure or vitamin D or A supplementation. He did not have any family history of hypercalcemia or renal stones.

Based on investigations (Table 1), the patient had a non-PTH mediated hypercalcemia with a suppressed PTH of 1.0 pmol/L (normal, 1.6 to 6.9 pmol/L), an elevated phosphate of 1.46 mmol/L (normal, 0.8 to 1.33 mmol/L), 25-vitamin D low at 54 nmol/L (normal, 75 to 250 nmol/L), 1,25-vitamin D of 205 pmol/L (normal, 60 to 208 pmol/L), normal thyroid-stimulating hormone of 1.85 mIU/L, angiotensin converting enzyme levels <8.0 U/L , a random cortisol of 515 nmol/L at 3:00 PM (normal, 133 to 537 nmol/L). His vitamin A levels were elevated at 4.6 μmol/L (normal, 1.2 to 2.8 μmol/L) with no history of excessive vitamin A intake or supplements. PTH-related peptide was 23 pg/mL (normal, 14 to 27 pg/mL). Twenty-four hour urine creatinine was 18.0 mmol/day (normal, 8.6 to 19.4 mmol/day) with an elevated 24-hour urine calcium level at 20.0 mmol/day (normal, 2.5 to 7.5 mmol/day). Bone marrow biopsy was nondiagnostic. Imaging with computed tomography (CT) of the head/chest/abdomen/pelvis was negative for malignancy. An initial renal biopsy showed focal segmental glomerulosclerosis and possible immunoglobulin A nephropathy. Repeat renal biopsy showed severe interstitial fibrosis and tubular atrophy.

A subsequent CT scan and bone scan were done 6 months later to rule out bony lesions and soft tissue injuries given his muscle pain and hypercalcemia. An unusual, striated pattern of the pectoralis muscles was visible at CT (Fig. 1), with symmetric, oval-shaped, fat density foci in the subcutaneous tissue and interposed between pectoralis muscle fibers. The fat density of the subcutaneous foci was assumed to be due to direct injection of paraffin oil. A bone scan (Fig. 2) demonstrated a pattern of metabolic bone disease with diffuse cortical bony activity in a pattern described as superscan due to renal osteodystrophy. This was more prominent in the thorax and upper extremities and around the knee, with soft tissue activity overlying the thorax. The overall pattern seen on imaging provided evidence for multiple paraffin oil self-injections in the pectoralis muscles which started prior to his first visit to

Table 1
Summary of Laboratory Results

Test	November 2016	September 2017	October 2017	March 2018	September 2018	January 2019
Calcium (2.15-2.55 mmol/L)	3.01	3.34	3.21	3.25	3.27	3.26
Albumin (35-50 g/L)	33	38	37	44	40	36
Phosphate (0.8-1.33 mmol/L)	2.71	1.46	1.14	1.59	1.80	1.47
PTH (1.6-6.9 pmol/L)	-	1.0	1.2	0.8	1.2	0.9
25-vitamin D (75-250 nmol/L)	-	54	62	43	51	96
1,25-hydroxyvitamin D (60-208 pmol/L)	-	205	201	155	208	244
Creatinine (62-120 μmol/L)	840	333	314	456	473	410

Abbreviation: PTH = parathyroid hormone.

the ED. Repeat blood work was consistent with a vitamin D-mediated hypercalcemia, likely from granulomatous inflammation caused by the paraffin oil injections.

In cases of granuloma formation from injections, the most effective therapy is moderate to high doses of glucocorticoids (2). The patient had experienced previous adverse effects to steroids, including acne, which made him reluctant to take them again. He was briefly trialed on denosumab injections, but found the effect of treatment to be modest and switched to pamidronate. Unfortunately, due to poor adherence with medical direction and multiple discharges against medical advice, management of his hypercalcemia has been challenging. Currently, he is continued on pamidronate infusions and inconsistent use of prednisone 20 mg once a day, with close monitoring of his calcium levels.

DISCUSSION

Hypercalcemia in granulomatous disease results from unregulated catalysis to 1,25-dihydroxyvitamin D by the enzyme, 1-alpha hydroxylase (CYP27B) (1). This extrarenal enzyme activity occurs within inflammatory cells, predominantly macrophages, and is not regulated by classic feedback controls, thereby allowing calcitriol and subsequently serum calcium levels to rise (3). Catabolism of calcitriol is regulated by 24-hydroxylase (CYP24A1), which is the rate limiting enzyme. Within macrophages, a missing or defective CYP24A1 enzyme can result in localized synthesis and accumulation of calcitriol in peripheral tissues. High dose glucocorticoids can be effective in these cases, as steroids can induce apoptosis of cells that produce CYP27B with a defective CYP24A1 enzyme, thereby, causing a decrease in calcitriol and subsequently calcium levels (1,4). Ketoconazole and infliximab have both been used in the treatment of sarcoidosis (5) and could be possible treatment considerations, but have not been described in this patient population and were not considered in our patient due to concerns with compliance. The cause of the elevated vitamin A levels was unclear but has been described in similar patients (2). We advised avoidance of vitamin A-rich foods, but felt that this was at most a minor contributor to the hypercalcemia.

Paraffin oil injections used subcutaneously for muscle augmentation can induce the formation of granulomatous and fibrotic skin reactions (paraffinomas). Recently, a few case reports have described non-PTH mediated hypercalcemia in such patients (2,6,7). A case series by Solling et al (2) reported 12 young bodybuilders with non-PTH mediated hypercalcemia using paraffin oil injections for muscle augmentation. These patients had biopsies from injection sites that suggested granuloma formation and elevated expression of 1-alpha hydroxylase activity, leading to increased intestinal calcium absorption causing hypercalcemia (2). A biopsy was not performed in our patient, as the imaging findings of granulomatous inflammation at multiple injection sites in the pectoralis muscles, along with the history of paraffin oil injection use strongly

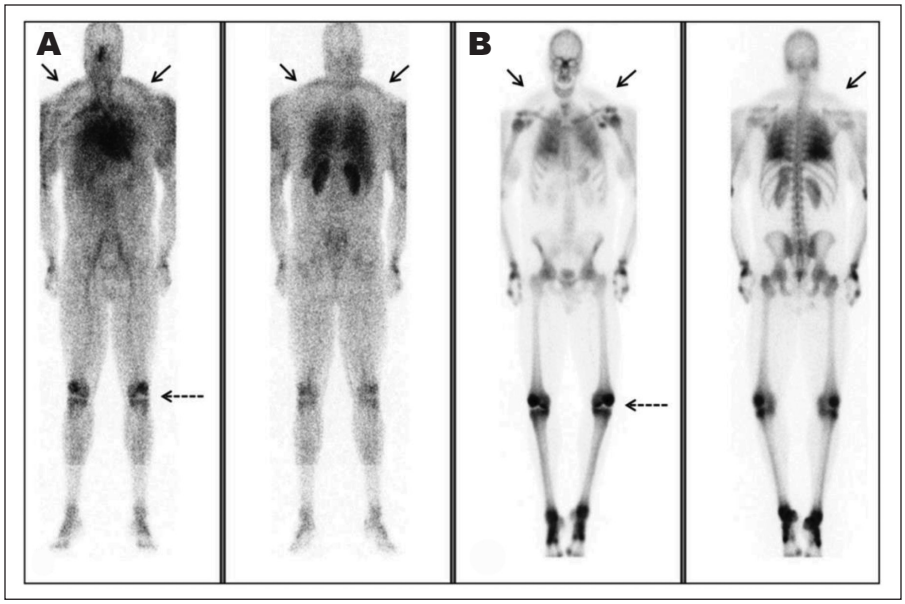

Fig. 1. A technetitium-99m-methyl diphosphonate (MDP) total body bone scan. *A*, Whole body blood pool; and *B*, Delayed images, of a 33-year-old male bodybuilder with severe hypercalcemia, suppressed PTH, elevated 1,25-vitamin D and renal impairment. *A*, Blood pool images demonstrate periarticular (dotted arrows) and diffuse thoracic and bilateral upper arm soft tissue hyperemia (solid arrows). *B*, Delayed images show prominent periarticular and cortical activity in the long bones (dotted arrows), low grade diffuse activity in the thoracic and upper arm muscles (solid arrows) and intense diffuse MDP distribution in the lungs and stomach confirmed by SPECT/CT (not shown). *CT* = computed tomography; *PTH* = parathyroid hormone; *SPECT* = single-photon emission computed tomography.

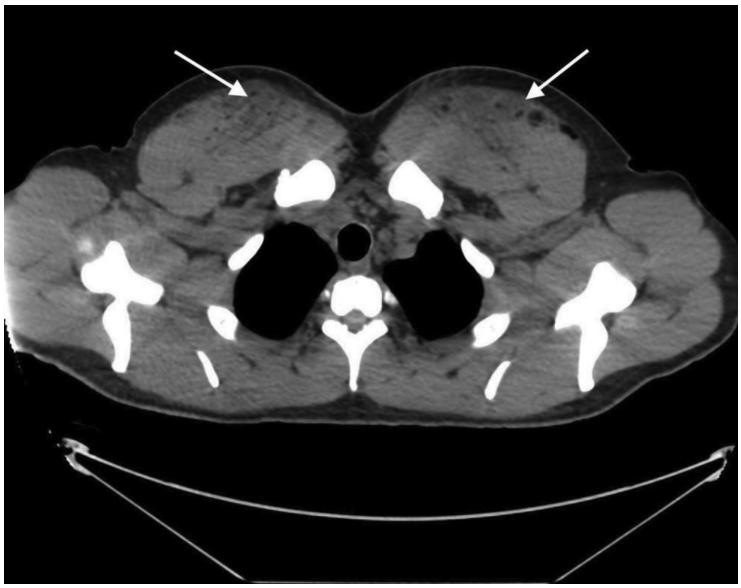

Fig. 2. Selected axial slice of noncontrast CT thorax demonstrates hypertrophy of pectoralis muscles (solid arrows) with multifocal ovoid areas of low density, thought to be secondary to previous paraffin oil injections (paraffinomas). *CT* = computed tomography.

suggested that granulomatous foreign body reaction was the most likely cause for hypercalcemia. The patient was then advised against the use of these injections. The time span for formation of these granulomas has been reported to be variable. One study by Tachamo et al (8), suggested a mean duration of 7.96 years from initial cosmetic injection to presentation of hypercalcemia.

Calcitriol levels were not always elevated for patients in these case reports, despite increased enzyme activity. It is possible that since these patients had low levels of 25-hydroxyvitamin D, even with increased activity of 1-alpha hydroxylase, the levels of 1,25-dihydroxyvitamin D were not significantly elevated, suggesting that perhaps the relative ratio might be more significant than the absolute values (9). A study by Tachamo et al (8) showed a significant response to treatment with steroids, and only a moderate response with antiresorptive medications. As calcium levels lowered with steroids, improvements were seen in renal function as well (8). Similar findings were also seen in our patient. Limited studies have reported surgical management of paraffinomas as a treatment in these cases. Tachamo et al (8), described 1 patient with a large area of granulomatous tissue surgically removed, with persistence of hypercalcemia postoperatively.

CONCLUSION

In this case report, we present a young bodybuilder with severe hypercalcemia and renal failure secondary to paraffin oil injections. Paraffinomas are a rare but important side effect of paraffin oil injections which can lead to serious long-term side effects of severe hypercalcemia. Prognosis is generally poor, with long term high-dose steroids as the current recommended treatment. Therefore, it is important to consider paraffin oil injection-related granulomas as a differential for non PTH-mediated hypercalcemia, especially in body builders.

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DISCLOSURE

The authors have no multiplicity of interest to disclose.

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